REMARKS

Claims 1-12, 15-19, and 21-27 were pending. Claims 15-17 and 19 are cancelled with this amendment. Claims 1, 4, 21, and 22 have been amended. Support for the amendments to the claims is found *inter alia* in the specification and claims as originally filed. For example, support for the amendments to claims 1, 4, and 22 is found at page 6, lines 14-17; and at p. 9, line 26 to p. 10, line 18. Support for the amendments to claim 21 is found at p. 9, line 26 to p. 10, line 20. No new matter is added by these amendments.

Applicants thank the Examiner for the courtesy of a telephonic interview on September 10, 2010 with Applicants' representative, Muriel Liberto, and Dr. Guy Vergnault, a co-inventor of the subject application. Dr. Vergnault explained how the claimed compositions and methods differ from the prior art of solid lipid nanoparticle ("SLN") formulations described by Mueller *et al*, *Eur. J. Pharmaceutics and Biopharma.* 50:161-177 (2000) ("Mueller"). Certain clarifying claim amendments were discussed but no specific agreement was reached. Instead, the Examiner said that Applicants should incorporate Dr. Vergnault's remarks into a written response along with amendments to the claims that would clarify the differences between the claimed compositions and SLN formulations.

In response to the objection to claim 19, Applicants note that this claim has been canceled, rendering the rejection moot.

Rejections under 35 U.S.C. § 103(a)

Claims 1-5, 8, 15-19, and 21-27 remain rejected as unpatentable over U.S. Patent No. 5,506,222 ("Stefano") in view of Mueller and further in view of the DrugBank entry for spironolactone, Mehnert *et al*, and zur Mtihlen *et al*. Claims 15-17 and 19 are cancelled with this amendment. The rejection is traversed to the extent it is applied to the remaining claims as amended.

Stefano is relied upon for describing a topical formulation of spironolactone. Office action at p. 5, first para. The Examiner characterizes Stefano as describing spironolactone "in a lipid matrix" referencing column 12, claim 2 of Stefano. Claim 2 describes a composition comprising a mixture of spironolactone and unsaturated fatty acids (as permeation enhancers). Stefano does not describe a *nanoparticulate* spironolactone formulation comprising nanoparticles of spironolactone *incorporated into a crystalline network of polar lipids*, as required by amended claims 1 and 22. By way of clarification, Applicants note that

the crystalline lipid structure required by the claims is formed from a mixture of a polar lipid in a polar liquid having the ability to form crystalline network structures from polar lipids. *See e.g.*, the specification at p. 9, line 26 to p. 10, line 3. The crystalline structure is formed upon the cooling of a molten mixture of the lipid in the polar liquid. Stefano neither describes nor suggests the incorporation of spironolactone into a lipid crystalline network, much less the incorporation of nanoparticulate spironolactone into such a crystal structure, as required by the amended claims.

Mueller is relied upon for describing solid lipid nanoparticles ("SLN"), their use in formulating drugs for various routes of administration, including topical, and methods for making SLN. Office action at p. 5, first para. However, the claimed compositions do not comprise SLN. Instead, the claimed compositions contain nanoparticles of spironolactone only, and not of lipid. The lipid of the claimed compositions is in the form of a crystalline structure created as a molten solution of the lipid in a polar liquid is cooled. *See e.g.*, the specification at p. 9, line 26 to p. 10, line 20.

To clarify the differences between the claimed compositions and SLN formulations, claims 1 and 22 have been amended to specify that the nanoparticulate spironolactone formulation comprises nanoparticles *of spironolactone incorporated into a crystalline network of polar lipids*. This amendment is also intended to clarify that the active of the claimed compositions is not contained within a solid lipid nanoparticle, as it must be in an SLN formulation. Instead, the active is incorporated into the lipid crystal structure. *See e.g.*, the specification at p. 10, lines 16-20. This is also distinct from a mere physical mixture of spironolactone and lipid such as is described by Stefano, as discussed above.

Claim 21 has been amended to further clarify the distinctions between the claimed process and the process for preparing SLN. Amended claim 21 specifies that the process comprises dispersing nanoparticulate spironolactone into a mixture of polar lipids and a polar liquid at a temperature below the transition temperature of the lipid but above the temperature at which the lipid crystalline structure is fully formed.

This process is distinct from the SLN processes described in Mueller. First, to form SLN containing the active, it is necessary to melt the lipid and then dissolve the active in the molten lipid. Mueller at p. 162, col. 2, para. 2. Then the drug-lipid solution is subjected to processes (such as homogenization) that create solid lipid nanoparticles containing the drug. Mueller at p. 162, col. 2, para. 2 to p. 163, para. 2. This is fundamentally different from the

claimed process, in which the active is not dissolved in the lipid but instead is dispersed into the mixture of lipid in a polar liquid as it cools, resulting in the incorporation of the nanoparticulate active into the lipid crystalline structure. *See e.g.*, the specification at p. 10, lines 16-27. In addition, according to the claimed methods, the lipid mixture is not subjected to processes that create nanoparticles, as it must be in the SLN process. Accordingly, the claimed methods do not produce solid lipid nanoparticles at all.

In summary, the combination of Stefano and Mueller as suggested by the Examiner would at most result in an SLN formulation of spironolactone. Since the claimed compositions are fundamentally different from SLN formulations, the combination of Stefano and Mueller does not render obvious independent claims 1, 21, and 22. In particular, the combination of Stefano and Mueller does not result in a *nanoparticulate* spironolactone formulation comprising *nanoparticles of spironolactone incorporated into a crystalline network of polar lipids*, as required by amended claims 1 and 22. With respect to claim 21, the combination of Stefano and Mueller does not describe a process comprising *dispersing nanoparticulate spironolactone into a mixture of polar lipids and a polar liquid at a temperature below the transition temperature of the lipid but above the temperature at which the lipid crystalline structure is fully formed.*

The remaining references cited by the Examiner do not overcome the deficiencies of Stefano and Mueller. The remaining rejected claims depend either directly or indirectly from claims 1, 21, or 22. Accordingly, a *prima facie* case of obviousness has not been established with respect to any of the rejected claims and Applicants request reconsideration and withdrawal of the rejections.

Applicants submit that the application is in condition for allowance and request an action for same. No fee, other than the fee for a one-month extension of time, is believed due in connection with the filing of this response. However, if any additional fee is required, please charge the amount of any such fee, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. **28069-608N01US**.

Respectfully submitted,

Date: September 13, 2010

David E. Johnson, Reg. No. 41,874
Muriel Liberto, Reg. No. 55,382
Attorneys for Applicants
C/O MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623

5020927v.2